

# **EXHIBIT AA**



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EXAMINER

WHISENANT, ETHAN C

ART UNIT

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Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. 10/661,165	Applicant(s) DHALLAN, RAVINDER S.	
	Examiner Ethan Whisenant, Ph.D.	Art Unit 1634	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 September 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-180 is/are pending in the application.
- 4a) Of the above claim(s) 153-155 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-98, 100-152 and 156-180 is/are rejected.
- 7) ☒ Claim(s) 99 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____  |

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**NON-FINAL ACTION**

1. Applicant's election of Group I ( **Claims 1-152 and 156-180** ) in the paper(s) filed 06 SEP 05 is acknowledged. Claims 153-155 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. It is noted that the applicant has not traversed the restriction requirement, distinctly and specifically pointing out any supposed errors in the restriction requirement, therefore, this election has been treated as an election without traverse (MPEP § 818.03(a)). The restriction requirement has been reconsidered, is deemed proper and is therefore, herein made **FINAL**.

**SEQUENCE RULES**

2. This application complies with the sequence rules and the sequences have been entered by the Scientific and Technical Information Center.

**35 USC § 112- 2nd Paragraph**

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**CLAIM REJECTIONS under 35 USC § 112- 2ND PARAGRAPH**

4. **Claim(s) 1-57, 103-142, 147, 149-151** is/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

**Claim 1** is indefinite in that it is unclear if the phrase "wherein said heterozygous locus of interest was identified by determining the sequence of alleles at a locus of interest from template DNA," recites a required positive step. Also, this claim fails to provide an adequate nexus between the preamble and the claim steps. Claim 1 in its preamble direct to a method which is to accomplish a particular goal, i.e. detect a chromosomal abnormality. However, the final claim steps states that the ratio indicates the

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presence or absence of a chromosomal abnormality. If the goal is not accomplished then there is a disconnect between the preamble and the claim steps. For clarity, claimed methods should recite that the purpose of the method has been attained (i.e. provide a nexus between the preamble and the claim steps). Please clarify. Inserting the phrase "detecting the presence or absence of a chromosomal abnormality" into the preamble would appear to overcome this portion of the 112, 2<sup>nd</sup> paragraph rejection.

**Claims 52, 103-131, 147** are indefinite because a trademark or trade name is included in the claim.

If a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of the 35 U.S.C. 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. In fact, the value of a trademark would be lost to the extent that it became descriptive of a product, rather than used as an identification of a source or origin of a product. Thus, the use of a trademark or trade name in a claim to identify or describe a material or product would not only render a claim indefinite, but would also constitute an improper use of the trademark or trade name. If a trademark or trade name appears in a claim and is not intended as a limitation in the claim, the question of why it is in the claim should be addressed. Does its presence in the claim cause confusion as to the scope of the claim? If so, the claim should be rejected under 35 U.S.C. 112, second paragraph.

**Claims 132-133** are indefinite in that the phrase "the annealed template and primer in step (4)" lacks proper antecedent basis.

**Claims 149** is indefinite in that the phrase "said agent is a cell lysis inhibitor" lacks proper antecedent basis in any of Claims 1, 132, 137, 139 or 141.

**Claims 151** is indefinite in that the phrase "the sample" lacks proper antecedent basis in any of Claims 1, 132, 138, 140 or 142.

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**35 USC § 102**

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that may form the basis for rejections set forth in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

or

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

6. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

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**CLAIM REJECTIONS UNDER 35 USC § 102**

**7. Claim(s) 1-4, 7-8, 52, 56-57 and 152** is/are rejected under 35 U.S.C. 102(e) as being anticipated by Antonarakis et al.[US 2005/0037388 (2005)].

**Claim 1** is drawn to a method for detecting the presence or absence a chromosomal abnormality which method comprises quantitating the relative amount of the alleles at a heterozygous locus of interest then expressing said relative amount as a ratio wherein said ratio indicates the presence or absence of said chromosomal abnormality.

Antonarakis et al. a teach method for detecting the presence or absence a chromosomal abnormality comprising all of the limitations recited in Claim 1-4, 7-8, 52, 56-57, and 152. See, at least, for example, the claims of Antonarakis et al.

**8. Claim(s) 87-95, 100 and 102** is/are rejected under 35 U.S.C. 102(b) as being anticipated by Lo et al. [WO98/39474 ( SEP 1998 )].

**Claim 87** is drawn to a method for preparing a sample for analysis comprising isolating free nucleic acid from a sample that contains nucleic acid wherein an agent that inhibits cell lysis has been added to the sample to inhibit cell lysis wherein said agent is selected from a defined group which includes a cell lysis inhibitor.

Lo et al. teach a method for preparing a sample for analysis comprising all of the limitations recited in Claims 87-95,100 and 102. Note pp. 6-8 wherein Lo et al. teach collecting maternal blood into a tube comprising EDTA (i.e. agent that inhibits cell lysis).

**9. Claim(s) 87-97, 100, 102** is/are rejected under 35 U.S.C. 102(b) as being anticipated by Schueler et al. [US2004/0185495 (2004)].

**Claim 87** is drawn to a method for preparing a sample for analysis comprising isolating free nucleic acid from a sample that contains nucleic acid wherein an agent that inhibits cell lysis has been added to the sample to inhibit cell lysis wherein said agent is selected from a defined group which includes a cell lysis inhibitor.

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Schueler et al. teach a method for preparing a sample for analysis comprising all of the limitations recited in Claims 87-97, 100, 102. Note especially Claims 91-92 wherein these authors teach treating the maternal blood with a solution comprising 4% formalin (i.e. agent that inhibits cell lysis).

**10.** Claim(s) **156-180** is/are rejected under 35 U.S.C. 102(b) as being anticipated by Jones et al. [US2003/0082576 (MAY 2003)].

**Claim 156-180** are drawn to a kit comprising a set of primers wherein the second primer contains a sequence that generates a recognition site for a restriction enzyme such that the restriction enzyme generates a 5' overhang containing the locus of interest, and a set of instructions

Jones et al. teach kits comprising primers useful for practicing the method(s) described in their patent application along with instructions for using the kit. As the method for determining a sequence of alleles at a locus of interest as broadly claimed in the instant claims is identical to one embodiment of the method disclosed by Jones et al., it can be said that Jones et al. anticipates the kit(s) of Claims 156-180.

### **35 USC § 103**

**11.** The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

**12.** This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

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**CLAIM REJECTIONS UNDER 35 USC § 103**

**13. Claim(s) 5-6** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al.[US 2005/0037388 (2005)].

Antonarakis et al. teach a method of detecting the presence or absence a chromosomal abnormality which comprises all of the limitations recited in Claims 5-6 except these authors do not teach analyzing multiple loci. However, as multiplexing (analyzing multiple loci simultaneously) was well known at the time of the invention as evidenced by a citation to a reference involving multiplexing - see, at least, for example, paragraph [0196] of Antonarakis et al. – it would have been, absent an unexpected result, *prima facie* obvious to of ordinary skill in the art at the time of the invention to modify the method of Antonarakis et al. wherein two or more of the loci disclosed by Antonarakis et al. are simultaneously analyzed. The motivation to multiplex the method of Antonarakis et al. would have been to gain as much information as possible in a single step about the chromosomal state of the fetus prior to making a diagnostic decision.

**14. Claim(s) 9-19** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al.[US 2005/0037388 (2005)] as applied against Claim 4 above and further in view of Schueler et al. [US 2004/0185495 (2004)] or Lo et al. [WO98/39474 ( SEP 1998)].

**Claim 9** is drawn to an embodiment of Claim 4 wherein the sample is mixed with an agent that inhibits cell lysis to inhibit the lysis of cells, if cells are present, wherein the agent is selected from a defined group which includes a membrane stabilizer and cell lysis inhibitor.

Antonarakis et al. teach a method of detecting the presence or absence a chromosomal abnormality which comprises all of the limitations recited in Claims 9-19 except these authors do not explicitly teach mixing their DNA containing sample(s) with an agent that inhibits cell lysis. However, as evidenced by both of Schueler et al. and Lo et al. it was well known at the time of the invention to add agents to biological sample which inhibit the lysis of the cells therein. See, at least, Claims 91-92 of Schueler et al. and pp. 6-8 of Lo et al. In light of these findings, and absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Antonarakis et al. wherein the cell isolation procedure of either of Schueler et al. or Lo et al. is used in place of the cell isolation procedure Antonarakis et al. Please note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the

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absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

**15. Claim(s) 58-62, 64-83** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al. [WO98/39474 ( SEP 1998)] in view of Wallace et al. [US 5,639,611 (1997)] or Jones et al. [US 2003/0082576 (2003)].

**Claim 58** is drawn to a method for determining the sequence of a locus of interest on free fetal DNA from a sample comprising free fetal DNA wherein an agent that inhibits cell lysis is added to said sample to inhibit the lysis of cells, if cells are present, wherein said agent is selected from a defined group which includes a cell lysis inhibitor.

Lo et al. teach a method for determining the sequence of a locus of interest on free fetal DNA comprising all of the limitations of Claim 58-62, 64-83 except these authors do not explicitly teach determining the sequence of a locus of interest. However, as evidenced by Wallace et al. or Jones et al. it was well known in the art at the time of the invention to determine the sequence of a locus of interest. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Lo et al. wherein the sequence of a locus of interest (i.e. the allele status of the  $\beta$ -globin gene) is determined. The ordinary artisan would have been motivated to make the above noted modification in order to determine the genotype of  $\beta$ -globin gene in the fetal DNA under investigation in Lo et al.

As regards the limitations present in Claims 67-68, it must be noted (Official Notice) that while neither of Lo et al. or Wallace et al. or Jones et al. do not explicitly teach testing the maternal and/or paternal DNA prior to testing the fetal DNA, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Lo et al. in view of Wallace et al. or Jones et al. wherein maternal and paternal DNA is tested prior to or simultaneously with the fetal DNA.

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16. **Claim(s) 63** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al. [WO98/39474 ( SEP 1998)] in view of Wallace et al. [US 5,639,611 (1997)] or Jones et al. [US 2003/0082576 (2003)] as applied against Claim 58 and 62 above and further in view of Schueler et al. [US 2004/0185495 (2004)].

**Claim 63** is drawn to an embodiment of Claim 62 wherein the cell lysis inhibitor is selected from a defined group which includes formalin.

Lo et al. in view of Wallace et al. or Jones et al. reasonably suggest a method for determining the sequence of a locus of interest on free fetal DNA comprising all of the limitations recited in Claim 63 except these authors do not teach adding gluteraldehyde, formaldehyde, derivatives thereof or formalin to the cell containing biological sample. However, Schueler et al. teach a method of adding formalin to a maternal blood sample during a method wherein fetal nucleic acids are analyzed. In light of these findings, and absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggest by the combination of Lo et al. in view of Wallace et al. or Jones et al. wherein the method of cell isolation of Schueler et al. is used instead of the cell isolation procedure(s) described in Lo et al. in view of Wallace et al. or Jones et al. Note that substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

17. **Claim(s) 101** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al. [WO98/39474 ( SEP 1998)] or Schueler et al. [US 2004/0185495 (2004)].

**Claim 101** is drawn to an embodiment of Claim 100 wherein the centrifugation step is performed with the centrifuge braking power set to zero.

Lo et al. and Schueler et al. both independently teach a method for preparing a sample for analysis comprising all of the limitations recited in Claim 101 except neither of these authors explicitly teach performing a centrifugation step wherein the centrifuge braking power is set to zero. However, it must be noted (Official Notice) that it was routine in the art to perform centrifugation step(s) wherein the centrifuge braking power set to zero. This is often done in steps involving DNA/RNA extraction with organic solvents in order to prevent disruption of the interface between the organic phase and the aqueous phase.

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**18. Claim(s) 156-180** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapero et al. [Genome Research 11 : 1926-1934 ( NOV 2001)] in view of the Stratagene Catalog (1988).

**Claim 156-180** are drawn to a kit comprising a set of primers wherein the second primer contains a sequence that generates a recognition site for a restriction enzyme such that the restriction enzyme generates a 5' overhang containing the locus of interest, and a set of instructions.

Shapero et al. teach a method which utilizes a set of primers wherein the second primer contains a sequence that generates a recognition site for a restriction enzyme such that the restriction enzyme generates a 5' overhang containing the locus of interest. Shapero et al. does not teach a kit. However, as evidenced by the Stratagene Catalog teaching, it was well known at the time of the invention to place the reagents needed to perform a nucleic acid based assay into a kit format. In addition, the Stratagene catalog teaches the advantages of assembling a kit, such as, saving resources and reducing waste. Therefore, absent an unexpected result, it would have been *prima facie* obvious to the ordinary artisan at the time of the invention to modify the teachings of Shapero et al. with the teachings of the Stratagene Catalog wherein the reagents necessary to perform the method taught by Shapero et al. are placed into a kit format. The ordinary artisan would have been motivated to make this modification in order to take advantage of the savings and efficiency afforded by kits. As regards the limitation that the kit contain instructions. Kits comprising instructions were well known at the time of the invention. Furthermore, it was well known at the time of the invention that kits should comprise instructions explaining how to use the kit.

**19. Claim(s) 1-8, 152** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. [US 6,100,029 (2000)].

Lapidus et al. teach a method for detecting a chromosomal abnormality which comprises all of the limitations set forth in Claims 1-8, 152 except these authors do not teach expressing the relative amount of alleles at a heterozygous locus as a ratio. These authors do teach that where there is an almost equal number of the two different labels (i.e. a 1 to 1 ratio of alleles) this indicates that there is normal heterozygosity at the polymorphic nucleotide. However where there is a statistically-significant difference between the detected numbers of the two labels, indicates that a deletion of the region encompassing the polymorphic nucleotide has occurred in one of the alleles. See at least, for example, Columns 1, line 64- Column 5, line 18. As the expression of two different corresponding measures as a ratio was well known at the time of the invention, see any Statistic textbook, it would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention to practice the method of Lapidus et al. wherein the relative amounts of the two different labels i.e. relative amounts of alleles at a heterozygous locus of interest is expressed as a ratio. The substitution of one well

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known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

**20. Claim(s) 9-19** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. [US 6,100,029 (2000)] as applied against Claim 4 above and further in view of Schueler et al. [US 2004/0185495 (2004)] or Lo et al. [WO98/39474 ( SEP 1998)].

**Claim 9** is drawn to an embodiment of Claim 4 wherein the sample is mixed with an agent that inhibits cell lysis to inhibit the lysis of cells, if cells are present, wherein the agent is selected from a defined group which includes a membrane stabilizer and cell lysis inhibitor.

Lapidus et al. reasonably suggest a method of detecting the presence or absence a chromosomal abnormality which comprises all of the limitations recited in Claims 9-19 except these authors do not explicitly teach mixing their DNA containing sample(s) with an agent that inhibits cell lysis. However, as evidenced by both of Schueler et al. and Lo et al. it was well known at the time of the invention to add agents to biological sample which inhibit the lysis of the cells therein. See, at least, Claims 91-92 of Schueler et al. and pp. 6-8 of Lo et al. In light of these findings, and absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Lapidus et al. wherein the cell isolation procedure of either of Schueler et al. or Lo et al. is used in place of the cell isolation procedure of Lapidus et al. Note that the substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

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**21. Claim(s) 20-21, 23-24, 27-30, 33-34, 37-39, 41, 44-52, 56-57** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. [US 6,100,029 (2000)] as applied against Claim 1 above and further in view of Jones et al. [US2003/0082576 (MAY 2003)].

**Claims 20-21** are drawn to embodiments of the method of Claim 1 wherein determining the sequence of the alleles is carried out by a particular method.

Lapidus et al. reasonably suggest a method of detecting the presence or absence a chromosomal abnormality which comprises all of the limitations recited in Claims 20-21, 23-24, 27-30, 33-34, 37-39, 41, 44-52 except these authors do not teach the same method of determining the sequence of the alleles at the heterozygous locus of interest recited in Claims 20-21. However, Jones et al. do teach the method for determining the sequence of the alleles at a heterozygous locus of interest recited in Claim 20-231. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Lapidus et al. wherein the SNP detection method of Jones et al. is used in place of the SNP detection method of Lapidus et al. The substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

**22. Claim(s) 22** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. [US 6,100,029 (2000)] in view of Jones et al. [US2003/0082576 (MAY 2003)] as applied against Claim 20-21 above and further in view of Western et al. [US 5,882,857 (1999)].

**Claims 22** are drawn to embodiment of the method of Claim 20 ore 21 wherein the incorporation of a nucleotide in ( c ) is by a DNA polymerase which DNA polymerase is selected from a defined group which includes Taq DNA polymerase

Lapidus et al. in view of Jones et al. reasonably suggest a method of detecting the presence or absence a chromosomal abnormality which comprises all of the limitations recited in Claims 22 except these authors do not explicitly teach the DNA polymerases recited in Claim 22. However, as each of the DNA polymerases recited were known at the time of the invention, see for example Western et al.- Column 16, beginning at about line 17 - it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of reasonably suggested by the combination of

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Lapidus et al. in view of Jones et al. wherein the DNA polymerase is one of those recited by Western et al. rather than the DNA polymerase taught by Jones et al. The substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

**23. Claim(s) 43** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. [US 6,100,029 (2000)] in view of Jones et al. [US2003/0082576 (MAY 2003)] as applied against Claim 20 and 21 above and further in view of MacLeod et al. [US 6,221,600 (2001)].

**Claims 43** are drawn to embodiments of the method of Claim 20 or 21 wherein the restriction enzyme site is for a restriction enzyme selected from a defined group.

Lapidus et al. in view of Jones et al. reasonably suggest a method of detecting the presence or absence a chromosomal abnormality which comprises all of the limitations recited in Claims 43 except these authors do not teach the same restriction enzymes recited in Claim 43. Jones et al. do teach a laundry list of possible restriction enzymes which can be used in their method but fail to explicitly recite those listed in Claim 43. However, as each of the restriction enzymes recited were known at the time of the invention, see for example MacLeod et al.- Table 1 - it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Lapidus et al. in view of Jones et al. wherein the restriction enzyme is one of those recited by MacLeod et al. rather than one of the restriction enzymes taught by Jones et al. The substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

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24. **Claim(s) 84-86** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Jones et al. [US2003/0082576 (MAY 2003)] in view of Lo et al. [WO98/39474 ( SEP 1998)].

**Claim 84** is drawn to a method for determining the sequence of a locus of interest in a sample comprising fetal DNA.

Jones et al. teach a method for determining the sequence of a locus of interest in a sample comprising all of the limitations recited in Claim 84-86 except these authors do not teach carrying out their analysis on fetal DNA. However, Lo et al. teach analyzing fetal DNA present in maternal blood in order to detect chromosomal aberrations prenatally. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Jones et al. wherein fetal DNA is analyzed. The motivation to make this modification would have been a desire to detect chromosomal aberrations. Furthermore, simply substituting fetal DNA for the DNA samples analyzed by Jones et al. would have been, absent an unexpected result, *prima facie* obvious to one of ordinary skill in the art at the time of the invention. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

25. **Claim(s) 143, 145** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lapidus et al. [US 6,100,029 (2000)] as applied against Claim 1 above and further in view of Schultz et al. [US 6,268, 146 (2001)].

**Claims 143** is drawn to embodiments of the method of Claim 1 wherein the SNP is detected by a method which appears to be real time PCR.

Lapidus et al. reasonably suggest a method of detecting the presence or absence a chromosomal abnormality which comprises all of the limitations recited in Claims 143 except these authors do not teach the same method (i.e. Real Time PCR) of determining the sequence of the alleles at the heterozygous locus of interest recited in Claim 1. However, Schultz et al. do teach detecting a SNP utilizing Real Time PCR. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Lapidus et al. wherein the SNP detection method of Schultz et al. is used in place of the SNP detection method of Lapidus et al. The substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art

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elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

**26. Claim(s) 144-146, 148-149** is/are rejected under 35 U.S.C. 103(a) as being unpatentable over Lo et al. [WO98/39474 ( SEP 1998)] in view of Wallace et al. [US 5,639,611 (1997)] or Jones et al. [US 5,639,611 (1997)] as applied against Claim 58 above and further in view of Schultz et al. [US 6,268, 146 (2001)].

**Claims 144** is drawn to embodiments of the method of Claim 58 wherein the sequence is detected by a method which appears to be real time PCR.

Lo et al. in view of Wallace et al. or Jones et al. reasonably suggest a method of determining the sequence of a locus of interest on fetal DNA which comprises all of the limitations recited in Claim 144 except these authors do not teach the same method (i.e. Real Time PCR) for determining the sequence of the alleles at the heterozygous locus of interest recited in Claim 144. However, Schultz et al. do teach detecting a sequence utilizing Real Time PCR. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method reasonably suggested by the combination of Lo et al. in view of Wallace et al. or Jones et al. wherein the SNP detection method of Schultz et al. is used in place of the SNP detection method of Wallace et al. or Jones et al. The substitution of one well known method/reagent with known properties for a second well known method/reagent with well known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

#### **Non-Statutory Obviousness-type Double Patenting Rejection**

**27.** The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982);

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*In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**28. Claim(s) 84 and 86** is/are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1 and 5 of U.S. 6,977,162.

The scope of Claim 84 of the instant application overlaps that of Claim 1 of U.S. Patent 6,977,162. The granting of a patent on Claim 84 would improperly extend the right to exclude previously granted in U.S. 6,977,162.

**29. Claim(s) 84 and 86** is/are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1 and 4 of U.S. Patent Application 11/107,624. This is a provisional obviousness-type double patenting rejection as the conflicting claims have not in fact been patented.

The broad scope of Claim 1 of U.S. Patent Application 11/107,624 encompasses the method for determining a sequence of a locus of interest recited in Claim 84 of U.S. Patent Application 11/107,624.

**30. Claim(s) 87 and 96-98** is/are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1 of U.S. Patent Application 11/212,386. This is a provisional obviousness-type double patenting rejection as the conflicting claims have not in fact been patented.

The scope of Claim 1 of U.S. Patent Application 11/212,386 overlaps that of Claim 98 of the instant application. Although not identical they are not patentably distinct.

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**CLAIM OBJECTIONS**

31. **Claim(s) 99** is objected to because it is dependent upon a rejected independent base claim.

**CONCLUSION**

32. **Claim(s) 1-152 and 156-180** is/are rejected and/or objected to for the reason(s) set forth above.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant, Ph.D. whose telephone number is (571) 272-0754. The examiner can normally be reached Monday-Friday from 8:30AM -5:30PM EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached at (571) 272-0745.

The Central Fax number for the USPTO is (571) 273-8300. Before faxing any papers, please inform the examiner to avoid lost papers. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

  
**ETHAN WHISENANT**  
**PRIMARY EXAMINER**

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